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EXAMINER

LIU, XUE H

ART UNIT

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PAPER

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

<b>Office Action Summary</b>	<b>Application No.</b> 10/590,316	<b>Applicant(s)</b> KAMMERMEIER ET AL.	
	<b>Examiner</b> XUE LIU	<b>Art Unit</b> 1742	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 22 April 2011.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 18-81 is/are pending in the application.
- 4a) Of the above claim(s) 34 and 38 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 18-33,35-37 and 39-81 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                     | 4) <input type="checkbox"/> Interview Summary (PTO-413)           |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____                                      |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)          | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____  | 6) <input type="checkbox"/> Other: _____                          |

***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/22/11 has been entered.

***Response to Amendment***

2. Amendment to claims filed 4/22/11 is acknowledged. Currently, claims 18-81 are pending. Claims 1-17 are cancelled. Claims 34-38 remain withdrawn. Claim 58 is currently amended.

***Claim Rejections - 35 USC § 103***

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

4. Claims 18-19, 21-27, 39-40 and 42-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann (US 6465226) in view of Kyekyoon et al. (WO02/13789)

Regarding claim 18, Zimmermann teaches a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising:

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(a) producing liquid aerosol droplets from a solution comprising an ionically crosslinkable polyionic polymer into a gas stream comprising compressed air and the droplets by using a nozzle;

(b) dropping the droplets carried by the gas stream into a gelling solution comprising bivalent or trivalent ions, whereby crosslinked polymer microspheres are formed (abstract, col. 2, lines 65 to col. 3, lines 29, col. 6, lines 38-45, col. 7, lines 28-31), and

(c) separating the microspheres from the gelling solution by centrifugation (see col. 3, ln. 25-29).

Zimmermann does not teach forming a continuous gas stream by using an ultrasonic nebulizer and transferring the gas stream into the gelling solution. However, Kyekyoon et al. teaches a method of forming particles by using an ultrasonic nebulizer (see fig. 7-8, page 14, "this approach represents an improvement over conventional ultrasonic nozzles..." and page 27, Example 1, "the acoustic excitation frequency was varied from 14 to 70 KHz... the sphere size increased with increasing polymer solution flow rate and decreasing ultrasound frequency") to nebulize a liquid into a continuous gas stream (see fig. 7 & 8 and page 19, ln. 10-13, "it is believed that the mechanical excitation launches a wave of acoustic energy along the liquid jet generating periodic instabilities that, in turn, break the stream into a train of droplets") and transferring the gas stream into a gelling solution (see fig. 7 & 8 and page 6, ln. 19-23, "the nozzle or orifice utilized is placed beneath the surface of an aqueous bath, to allow hardening of the spheres with a minimum of deformation"). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Zimmermann's process with Kyekyoon et al. since Kyekyoon et al. offers a solution for a microencapsulation process that produces

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microparticles of precisely controlled sizes and size distributions for biomedical applications including passive or active targeting to desired cells, tissue or regions of the body (see page 7, ln. 1-8).

Regarding claim 19, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises a polyvalent cation (abstract, col. 4, lines 18-19, col. 6, lines 9-22 and 43-45).

Regarding claim 21, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises di-, multi- or polyvalent cations (col. 4, lines 18-19 and col. 6, lines 38-45).

Regarding claims 22-24, Zimmermann teaches that the polyanionic polymer is alginate (abstract, col. 6, lines 9-21 and col. 7, lines 28-31), which is a salt of alginic acid.

Regarding claim 25, Zimmermann teaches that in step (a), the polyanionic polymer is present in a concentration of less than 5% by weight (col. 2, lines 56-63).

Regarding claims 26-27, Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations (col. 6, lines 39-42).

Regarding claim 39, the claim is identical to claim 18 except for the additional limitation of "submerging the gas stream via a tubing comprising dispenser holes into a gelling solution". Zimmermann as modified by Kyekyoon et al. teaches this limitation. See Kyekyoon et al., fig. 8, and page 6, ln.18-22, "the nozzle or orifice utilized is placed beneath the surface of an aqueous bath, to allow hardening of the spheres with a minimum of deformation").

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Regarding claim 40, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises a polyvalent cation (abstract, col. 4, lines 18-19, col. 6, lines 9-22 and 43-45).

Regarding claim 42, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises di-, multi- or polyvalent cations (col. 4, lines 18-19 and col. 6, lines 38-45).

Regarding claims 43-45, Zimmermann teaches that the polyanionic polymer is alginate (abstract, col. 6, lines 9-21 and col. 7, lines 28-31), which is a salt of alginic acid.

Regarding claim 46, Zimmermann teaches that in step (a), the polyanionic polymer is present in a concentration of less than 5% by weight (col. 2, lines 56-63).

Regarding claim 47-48, Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations (col. 6, lines 39-42).

5. Claims 20, 28, 41 and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Kyetyoon et al. as applied to claim 19 or 39 above, and further in view of Lim (US 4,352,883).

Regarding claim 20 and 41, Zimmermann does not teach that the polyvalent cation of the gelling solution is selected from the group consisting of poly (allylamine hydrochloride), poly (ethylene imine), poly (diallyldimethylammonium chloride), polyamide-polyamine-epichlorhydrine, chitosan, amino-dextran, and protamine sulfate.

However, Lim teaches that the polyvalent cation of the gelling solution is polyethyleneimine (col. 7, lines 59-64).

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It would have been obvious to one of ordinary skill in the art at the time of the invention to select polyethyleneimine as the polyvalent cation in the gelling solution in the method of Zimmermann since Lim teaches that polysaccharide can be (a) gelled to form a shape retaining mass by being exposed to a change in conditions such a pH change or by being exposed to multivalent cations such as  $\text{Ca}^{++}$ ; and (b) permanently “crosslinked” or hardened by polymers containing reactive groups such as amine or imine groups which can react with acidic polysaccharide constituents (col. 2, lines 37-46).

Regarding claims 28 and 49, Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations.

Zimmermann does not positively teach that the metal cation of the gelling solution is  $\text{Ca}^{2+}$ .

However, Lim teaches that  $\text{Ca}^{2+}$  is used as the metal cation of the gelling solution (col. 2, lines 37-42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select  $\text{Ca}^{2+}$  as the metal cation of the gelling solution in the method of Zimmermann since Lim teaches that  $\text{Ca}^{2+}$  is a multivalent cation which forms crosslinked polymer microspheres with polysaccharide (col. 2, lines 37-42). The Ca cation is viewed as functional equivalent, providing gel.

6. Claims 29-30, 32, 35-37, 50-51, 53 and 55-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Kyetyoon et al. as applied to claim 18 or 39 above, and further in view of Andersson et al. (WO 03/091315).

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Regarding claims 29-30 and 36, Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Additionally the amount of surfactant is known to affect particle size of the capsules.

Regarding claim 32 and 37, Zimmerman does not positively teach that the temperature of the solution of the ionically crosslinkable polyionic polymer according to step (a) is kept within a temperature of from 25 to 35 deg C. However, Andersson et al. teach the temperature of the polysaccharide solution should be kept low, such as below about 40 deg C (page 5, lines 2-4). It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann since Andersson et al. teach that keeping the solution at a low temperature avoids formation of lumps (page 5, lines 2-4).

Regarding claim 35, Zimmerman does not teach filtering the microspheres through a screen.

However, Andersson et al. teach filtering the beads to a sieve 14 for particle concentration (page 13, line 5 and fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the filtering step as taught by Andersson et al. in the method of Zimmermann in order to obtain microspheres with a more uniform size distribution.

Regarding claims 50-51 and 56, Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line 25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Additionally the amount of surfactant is known to affect particle size of the capsules.

Regarding claim 53 and 57, Zimmerman does not positively teach that the temperature of the solution of the ionically crosslinkable polyionic polymer according to step (a) is kept within a temperature of from 25 to 35 deg C. However, Andersson et al. teach the temperature of the polysaccharide solution should be kept low, such as below about 40 deg C (page 5, lines 2-4). It would have been obvious to one of ordinary skill in the art at the time of the invention to

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incorporate the teaching of Andersson et al. in the method of Zimmermann since Andersson et al. teach that keeping the solution at a low temperature avoids formation of lumps (page 5, lines 2-4).

Regarding claim 55, Zimmerman does not teach filtering the microspheres through a screen.

However, Andersson et al. teach filtering the beads to a sieve 14 for particle concentration (page 13, line 5 and fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the filtering step as taught by Andersson et al. in the method of Zimmermann in order to obtain microspheres with a more uniform size distribution.

7. Claims 31, 52 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmerman in view of Kyetyoon et al. and Andersson et al. as applied to claim 29, 50 or 78 above, and further in view of Lemoine et al. NPL document Preparation and characterization of alginate microspheres containing a model antigen).

Regarding claims 31, 52 and 79, Andersson et al. do not positively teach that the surfactant is selected from the group consisting of polyoxyethylene sorbitans and surfactants comprising a block copolymer of ethylene oxide and/or propylene oxide.

However, Lemoine et al. teach the use of polyoxyethylene sorbitan trioleate as surfactant in the production of alginate microspheres (see section 2.1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polyoxyethylene sorbitan trioleate as surfactant in the method of Zimmermann since

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Lemoine et al. teach that polyoxyethylene sorbitan trioleate, or Tween 85 produced less heterogeneous and smaller microspheres (table 1 and section 3.1). Surfactant of Lemoine is viewed as functional equivalent.

8. Claims 33 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Kyekyoon et al. as applied to claim 21 or 42 above, and further in view of Vasington et al. (US 5,387,522), Andersson et al. (WO 03/091315) and Lemoine et al. NPL document Preparation and characterization of alginate microspheres containing a model antigen).

Regarding claims 33 and 54, Zimmermann teaches that in step (a), the solution comprises about 2 % by weight sodium alginate (col. 2, lines 56-63). Zimmermann does not teach that the solution comprises of from 0.75% to 1.5% by weight of sodium alginate. Zimmermann does not positively teach that the sodium alginate is low viscosity.

However, Vasington et al. teach low viscosity sodium alginates that are used as the polyanionic polymer. Further, Vasington et al. teach that the concentration of the sodium alginates in the mixture should range from about 0.5 to about 1.4%, preferably about 0.6 to 1.2%, most preferably about 0.7-0.9% (col. 5, lines 17-51).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Vasington et al. in the method of Zimmerman et al. since Vasington et al. teach that low percentage of sodium alginate result in higher porosity of the gel beads to nutrients and other factors (col. 5, line 46-51). Moreover, lowering the viscosity of sodium alginates produces smaller microspheres. Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $Ba^{2+}$  and other bivalent cations. Zimmermann does not

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positively teach that the metal cation of the gelling solution is  $\text{Ca}^{2+}$ . However, Vasington et al. teach that the cation in the gelling solution is  $\text{Ca}^{2+}$  (col. 6, lines 46-48, col. 7, lines 28-32 and col. 8, lines 42-47).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use  $\text{Ca}^{2+}$  as the cation in the gelling solution as taught by Vasington et al. since Vasington et al. teach that  $\text{Ca}^{2+}$  forms stable calcium alginate gel containing entrapped cells (col. 8, lines 42-47).

Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line 25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Andersson et al. do not positively teach that the surfactant is poly (oxyethylene) 20-sorbitane monolaurate.

However, Lemoine et al. teach the use of polyoxyethylene sorbitan trioleate as surfactant in the production of alginate microspheres (see section 2.1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polyoxyethylene sorbitan trioleate as surfactant in the method of Zimmermann since Lemoine et al. teach that polyoxyethylene sorbitan trioleate, or Tween 85 produced less heterogeneous and smaller microspheres (table 1 and section 3.1).

While Andersson et al. teach the use of polyoxyethylene sorbitan trioleate, as opposed to poly (oxyethylene) 20-sorbitane monolaureate as recited in claim 33.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute polyoxyethylene sorbitan trioleate with poly (oxyethylene) 20-sorbitane monolaureate since both surfactants are structurally similar.

9. Claims 58-64 and 65 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann (US 6465226) in view of Kyekyoon et al. (WO 02/13786), Lim (US 4,352,883), Andersson et al. (WO 03/091315) and Lemoine et al. NPL document Preparation and characterization of alginate microspheres containing a model antigen).

Regarding claims 58-61 and 64, Zimmermann teaches a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising:

(a) producing liquid aerosol droplets from a solution comprising an ionically crosslinkable polyionic polymer into a gas stream comprising compressed air and the droplets by using a nozzle;

(b) dropping the droplets carried by the gas stream into a gelling solution comprising bivalent or trivalent ions, whereby crosslinked polymer microspheres are formed (abstract, col. 2, lines 65 to col. 3, lines 29, col. 6, lines 38-45, col. 7, lines 28-31), and

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(c) separating the microspheres from the gelling solution by centrifugation (see col. 3, ln. 25-29).

Zimmermann does not teach forming a continuous gas stream by using an ultrasonic nebulizer and submerging the gas stream into the gelling solution. However, Kyekyoon et al. teaches a method of forming particles by using an ultrasonic nebulizer (see fig. 7-8, page 14, "this approach represents an improvement over conventional ultrasonic nozzles..." and page 27, Example 1, "the acoustic excitation frequency was varied from 14 to 70 KHz... the sphere size increased with increasing polymer solution flow rate and decreasing ultrasound frequency") to nebulize a liquid into a continuous gas stream (see fig. 7 & 8 and page 19, ln. 10-13, "it is believed that the mechanical excitation launches a wave of acoustic energy along the liquid jet generating periodic instabilities that, in turn, break the stream into a train of droplets") and submerging the gas stream into a gelling solution (see fig. 7 & 8 and page 6, ln. 19-23, "the nozzle or orifice utilized is placed beneath the surface of an aqueous bath, to allow hardening of the spheres with a minimum of deformation"). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Zimmermann's process with Kyekyoon et al. since Kyekyoon et al. offers a solution for a microencapsulation process that produces microparticles of precisely controlled sizes and size distributions for biomedical applications including passive or active targeting to desired cells, tissue or regions of the body (see page 7, ln. 1-8).

Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations.

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Zimmermann does not positively teach that the metal cation of the gelling solution is  $\text{Ca}^{2+}$ .

However, Lim teaches that  $\text{Ca}^{2+}$  is used as the metal cation of the gelling solution (col. 2, lines 37-42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select  $\text{Ca}^{2+}$  as the metal cation of the gelling solution in the method of Zimmermann since Lim teaches that  $\text{Ca}^{2+}$  is a multivalent cation which forms crosslinked polymer microspheres with polysaccharide (col. 2, lines 37-42). The Ca cation is viewed as functional equivalent, providing gel.

Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line 25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Andersson et al. do not positively teach that the surfactant is poly (oxyethylene) 20-sorbitane monolaureate.

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However, Lemoine et al. teach the use of polyoxyethylene sorbitan trioleate as surfactant in the production of alginate microspheres (see section 2.1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polyoxyethylene sorbitan trioleate as surfactant in the method of Zimmermann since Lemoine et al. teach that polyoxyethylene sorbitan trioleate, or Tween 85 produced less heterogeneous and smaller microspheres (table 1 and section 3.1).

While Andersson et al. teach the use of polyoxyethylene sorbitan trioleate, as opposed to poly (oxyethylene) 20-sorbitane monolaureate as recited in claim 58; it would have been obvious to one of ordinary skill in the art at the time of the invention to substitute polyoxyethylene sorbitan trioleate with poly (oxyethylene) 20-sorbitane monolaureate since both surfactants are structurally similar.

Regarding claim 62 and 65, Zimmerman does not positively teach that the temperature of the solution of the ionically crosslinkable polyionic polymer according to step (a) is kept within a temperature of from 25 to 35 deg C. However, Andersson et al. teach the temperature of the polysaccharide solution should be kept low, such as below about 40 deg C (page 5, lines 2-4). It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann since Andersson et al. teach that keeping the solution at a low temperature avoids formation of lumps (page 5, lines 2-4).

Regarding claim 63, Zimmerman does not teach filtering the microspheres through a screen.

However, Andersson et al. teach filtering the beads to a sieve 14 for particle concentration (page 13, line 5 and fig. 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the filtering step as taught by Andersson et al. in the method of Zimmermann in order to obtain microspheres with a more uniform size distribution.

10. Claims 66-67, 69-75, 77-78 and 81 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann (US 6465226) in view of Kyekyoon et al. (WO 02/13786), and Andersson et al. (WO 03/091315).

Regarding claim 66, Zimmermann teaches a process for preparing microspheres comprising an ionically crosslinked polymer, the process comprising:

(a) producing liquid aerosol droplets from a solution comprising an ionically crosslinkable polyionic polymer into a gas stream comprising compressed air and the droplets by using a nozzle;

(b) dropping the droplets carried by the gas stream into a gelling solution comprising bivalent or trivalent ions, whereby crosslinked polymer microspheres are formed (abstract, col. 2, lines 65 to col. 3, lines 29, col. 6, lines 38-45, col. 7, lines 28-31), and

(c) separating the microspheres from the gelling solution by centrifugation (see col. 3, ln. 25-29).

Zimmermann does not teach forming a continuous gas stream by using an ultrasonic nebulizer and submerging the gas stream into the gelling solution. However, Kyekyoon et al. teaches a method of forming particles by using an ultrasonic nebulizer (see fig. 7-8, page 14, "this approach represents an improvement over conventional ultrasonic nozzles..." and page 27,

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Example 1, "the acoustic excitation frequency was varied from 14 to 70 KHz... the sphere size increased with increasing polymer solution flow rate and decreasing ultrasound frequency") to nebulize a liquid into a continuous gas stream (see fig. 7 & 8 and page 19, ln. 10-13, "it is believed that the mechanical excitation launches a wave of acoustic energy along the liquid jet generating periodic instabilities that, in turn, break the stream into a train of droplets") and submerging the gas stream into a gelling solution (see fig. 7 & 8 and page 6, ln. 19-23, "the nozzle or orifice utilized is placed beneath the surface of an aqueous bath, to allow hardening of the spheres with a minimum of deformation"). It would have been obvious to one of ordinary skill in the art at the time of the invention to modify Zimmermann's process with Kyekyoon et al. since Kyekyoon et al. offers a solution for a microencapsulation process that produces microparticles of precisely controlled sizes and size distributions for biomedical applications including passive or active targeting to desired cells, tissue or regions of the body (see page 7, ln. 1-8).

Zimmerman does not positively teach that the temperature of the solution of the ionically crosslinkable polyionic polymer according to step (a) is kept within a temperature of from 25 to 35 deg C. However, Andersson et al. teach the temperature of the polysaccharide solution should be kept low, such as below about 40 deg C (page 5, lines 2-4). It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann since Andersson et al. teach that keeping the solution at a low temperature avoids formation of lumps (page 5, lines 2-4).

Regarding claim 67, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises a polyvalent cation (abstract, col. 4, lines 18-19, col. 6, lines 9-22 and 43-45).

Regarding claim 69, Zimmermann teaches that the ionically crosslinkable polymer is a polyanionic polymer and the gelling solution comprises di-, multi- or polyvalent cations (col. 4, lines 18-19 and col. 6, lines 38-45).

Regarding claims 70-72, Zimmermann teaches that the polyanionic polymer is alginate (abstract, col. 6, lines 9-21 and col. 7, lines 28-31), which is a salt of alginic acid.

Regarding claim 73, Zimmermann teaches that in step (a), the polyanionic polymer is present in a concentration of less than 5% by weight (col. 2, lines 56-63).

Regarding claims 74-75, Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations (col. 6, lines 39-42).

Regarding claims 77-78, Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line 25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of

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surfactant to satisfactorily lower the surface tension of the solution. Additionally the amount of surfactant is known to affect particle size of the capsules.

Regarding claim 81, Zimmermann does not positively teach that the temperature of the solution of the ionically crosslinkable polyionic polymer according to step (a) is kept within a temperature of from 25 to 35 deg C. However, Andersson et al. teach the temperature of the polysaccharide solution should be kept low, such as below about 40 deg C (page 5, lines 2-4). It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann since Andersson et al. teach that keeping the solution at a low temperature avoids formation of lumps (page 5, lines 2-4).

11. Claims 68 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Andersson and Kyekyoon et al. as applied to claim 67 or 75 above, and further in view of Lim (US 4,352,883).

Regarding claim 68, Zimmermann does not teach that the polyvalent cation of the gelling solution is selected from the group consisting of poly (allylamine hydrochloride), poly (ethylene imine), poly (diallyldimethylammonium chloride), polyamide-polyamine-epichlorhydrine, chitosan, amino-dextran, and protamine sulfate.

However, Lim teaches that the polyvalent cation of the gelling solution is polyethyleneimine (col. 7, lines 59-64).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select polyethyleneimine as the polyvalent cation in the gelling solution in the method of Zimmermann since Lim teaches that polysaccharide can be (a) gelled to form a shape retaining

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mass by being exposed to a change in conditions such a pH change or by being exposed to multivalent cations such as  $\text{Ca}^{++}$ ; and (b) permanently “crosslinked” or hardened by polymers containing reactive groups such as amine or imine groups which can react with acidic polysaccharide constituents (col. 2, lines 37-46).

Regarding claim 76, Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations.

Zimmermann does not positively teach that the metal cation of the gelling solution is  $\text{Ca}^{2+}$ .

However, Lim teaches that  $\text{Ca}^{2+}$  is used as the metal cation of the gelling solution (col. 2, lines 37-42).

It would have been obvious to one of ordinary skill in the art at the time of the invention to select  $\text{Ca}^{2+}$  as the metal cation of the gelling solution in the method of Zimmermann since Lim teaches that  $\text{Ca}^{2+}$  is a multivalent cation which forms crosslinked polymer microspheres with polysaccharide (col. 2, lines 37-42). The Ca cation is viewed as functional equivalent, providing gel.

12. Claim 80 is rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann in view of Kyekyoon et al. and Andersson as applied to claim 69 above, and further in view of Vasington et al. (US 5,387,522), and Lemoine et al. NPL document Preparation and characterization of alginate microspheres containing a model antigen).

Regarding claim 80, Zimmermann teaches that in step (a), the solution comprises about 2 % by weight sodium alginate (col. 2, lines 56-63). Zimmermann does not teach that the solution

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comprises of from 0.75% to 1.5% by weight of sodium alginate. Zimmermann does not positively teach that the sodium alginate is low viscosity.

However, Vasington et al. teach low viscosity sodium alginates that are used as the polyanionic polymer. Further, Vasington et al. teach that the concentration of the sodium alginates in the mixture should range from about 0.5 to about 1.4%, preferably about 0.6 to 1.2%, most preferably about 0.7-0.9% (col. 5, lines 17-51).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Vasington et al. in the method of Zimmerman et al. since Vasington et al. teach that low percentage of sodium alginate result in higher porosity of the gel beads to nutrients and other factors (col. 5, line 46-51). Moreover, lowering the viscosity of sodium alginates produces smaller microspheres. Zimmermann teaches that the ion of the gelling solution is a metal cation such as  $\text{Ba}^{2+}$  and other bivalent cations. Zimmermann does not positively teach that the metal cation of the gelling solution is  $\text{Ca}^{2+}$ . However, Vasington et al. teach that the cation in the gelling solution is  $\text{Ca}^{2+}$  (col. 6, lines 46-48, col. 7, lines 28-32 and col. 8, lines 42-47).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use  $\text{Ca}^{2+}$  as the cation in the gelling solution as taught by Vasington et al. since Vasington et al. teach that  $\text{Ca}^{2+}$  forms stable calcium alginate gel containing entrapped cells (col. 8, lines 42-47).

Zimmermann does not teach that the gelling solution additionally comprises a surfactant present in an amount of from 0.05 to .15% by weight.

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However, Andersson et al. teach that droplets which form polysaccharide beads are collected in a bath comprised of a liquid having a reduced surface tension by adding a surfactant to the liquid (page 7, line 25- page 8, line 1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the teaching of Andersson et al. in the method of Zimmermann to provide a surfactant in the gelling solution to facilitate movement of the beads in the solution.

Andersson et al. do not positively teach the amount of surfactant that is added, however, it would have been obvious to one of ordinary skill in the art to select an appropriate amount of surfactant to satisfactorily lower the surface tension of the solution. Andersson et al. do not positively teach that the surfactant is poly (oxyethylene) 20-sorbitane monolaureate.

However, Lemoine et al. teach the use of polyoxyethylene sorbitan trioleate as surfactant in the production of alginate microspheres (see section 2.1).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use polyoxyethylene sorbitan trioleate as surfactant in the method of Zimmermann since Lemoine et al. teach that polyoxyethylene sorbitan trioleate, or Tween 85 produced less heterogeneous and smaller microspheres (table 1 and section 3.1).

While Andersson et al. teach the use of polyoxyethylene sorbitan trioleate, as opposed to poly (oxyethylene) 20-sorbitane monolaureate as recited in claim 33.

It would have been obvious to one of ordinary skill in the art at the time of the invention to substitute polyoxyethylene sorbitan trioleate with poly (oxyethylene) 20-sorbitane monolaureate since both surfactants are structurally similar.

***Response to Arguments***

13. Applicant's arguments with respect to claims 18, 34, 39, 58 and 66 have been considered but are moot in view of the new ground(s) of rejection.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to XUE LIU whose telephone number is (571)270-5522. The examiner can normally be reached on Monday to Friday 9:30 - 6:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Johnson can be reached on (571)272-1176. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/X. L./

Examiner, Art Unit 1742

/Christina Johnson/

Supervisory Patent Examiner, Art Unit 1742